

activated T cells to enhance their ability to mediate tumor destruction. Although **adoptive** immunotherapy has thus far added little to the routine treatment of human cancer, it is likely that continued efforts at defining the elements involved in **T cell** recognition and destruction of **tumor cells** will broaden the applicability of **T cells** as important **therapeutic** reagents.

**Costimulation of tumor-reactive CD4+ and CD8+ T lymphocytes by B7, a natural ligand for CD28, can be used to treat established mouse melanoma.**

Li Y; McGowan P; Hellstrom I; Hellstrom K E; Chen L

Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, WA 98121.

Journal of immunology (Baltimore, Md. : 1950) (UNITED STATES) Jul 1 1994, 153 (1) p421-8, ISSN 0022-1767 Journal Code: 2985117R

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Interactions between the costimulatory molecule B7 on APC and its counter-receptor CD28 on T lymphocytes play a key role in the induction of cell-mediated **retroviral transduction of interferon-gamma cDNA into a nonimmunogenic murine fibrosarcoma: generation of T cells in draining lymph nodes capable of treating established parental metastatic tumor.**

Shiloni E; Karp S E; Custer M C; Shilyansky J; Restifo N P; Rosenberg S A ; Mule J J

Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892.

Cancer immunology, immunotherapy : CII (GERMANY) Oct 1993, 37 (5) p286-92, ISSN 0340-7004 Journal Code: 8605732

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Gene modification of tumor cells with the cDNA for interferon gamma (IFN gamma) has been shown to increase the immunogenicity of some tumor cells. In order to explore further the possible therapeutic relevance of these previous findings, two clones of the nonimmunogenic MCA-102 fibrosarcoma of C57BL/6 origin were retrovirally transduced with the cDNA encoding murine IFN gamma: 102.4JK (4JK), a clone with relatively high major histocompatibility complex (MHC) class I expression. **Activation of CD8+ murine T cells from tumor phorbol dibutyrate plus calcium ionophore.**

Tuttle T M; Inge T H; McCrady C M; Bethke K P; Bear H D

Department of Surgery, Massey Cancer Center, Medical College of Virginia, Richmond 23298.

Journal of immunotherapy : official journal of the Society for Biological Therapy (UNITED STATES) Jul 1992, 12 (1) p32-40, ISSN 1053-8550  
Journal Code: 9102704

Contract/Grant No.: CA48075; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

When lymphocytes from the lymph **IL-2: a review of current knowledge.**

Oldham R K; Maleckar J R; Yannelli J R; West W H

Biotherapeutics, Inc., Cellular Immunology Section, Franklin, Tennessee 37064.

Cancer treatment reviews (ENGLAND) Jun 1989, 16 Suppl A p5-13, ISSN 0305-7372 Journal Code: 7502030

Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

**Adoptive T-cell immunotherapy of cancer.**

Li Q; Chang A E

Division of Surgical Oncology, University of Michigan, Ann Arbor, USA.

Cytokines Cell Mol Ther (ENGLAND) Jun 1999, 5 (2) p105-17, ISSN 1368-4736 Journal Code: 9713367

Document Type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

**Adoptive T - cell therapy** involves the passive transfer of antigen-reactive **T cells** to a **tumor**-bearing host in order to initiate tumor rejection. Based upon animal models, effector T cells with tumor-specific reactivity are superior to non-specific effector T cells in mediating tumor regression in vivo. Both CD4+ and CD8+ T cells are capable of initiating tumor rejection after **adoptive** transfer. Several different **culture** methods have been reported that permit **in vitro** expansion of immune T cells while retaining tumor specificity. The ability to generate human tumor-specific effector T cells capable of mediating tumor rejection in vivo has provided tools to identify tumor-associated antigens. Future directions in this field involve the selective isolation and expansion of subpopulations of T cells critical to initiating tumor rejection, and the use of molecular techniques to generate effector T cells.

**adoptive -transfer therapy of tumors with the tumor -specific primary cytotoxic T cells induced in vitro with the B7.1-transduced MCA205 cell line**

Sun Jung Kim; Sadelain M.; Lee J.-S.; Roh Hyun Seong; Yun Y.-S.; Young Ju Jang; Hee-Yong Chung

H.Y. Chung, Laboratory of Tumor Immunology, Korea Cancer Center Hospital, Nowon-Gu, Gongneung 2 Dong, 215-4, Seoul 139-706 South Korea

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Cancer Immunology Immunotherapy ( CANCER IMMUNOL. IMMUNOTHER. ) (Germany) 1999, 47/5 (257-264)

CODEN: CIIMD ISSN: 0340-7004

DOCUMENT TYPE: Journal; Article

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

NUMBER OF REFERENCES: 30

We show that the tumor-specific primary cytotoxic T lymphocytes (CTL) induced in vitro with the MCA205 fibrosarcoma cells transduced with the B7.1 (CD80) gene are highly effective in adoptive-transfer therapy of the parental tumors. The MCA205 fibrosarcoma cell line was transduced with the retroviral vectors encoding the B7.1 gene and tested for their efficiency as stimulators in short-term (5 days) mixed lymphocyte/tumor cell cultures with highly purified syngenic, unprimed T cells as responders. The induction of the CTL required the presence of a low dose of interleukin-2 (25 U/ml). The injection of the CTL prevented colony formation by the intravenously injected tumor cells in a lung colonization assay in which the CTL were injected after inoculation of tumor cells. We also showed that the adoptive transfer of the same T cells was effective in delaying the growth of the subcutaneously injected tumor cells. These results imply that the short-term mixed lymphocyte/tumor cell culture with the tumor cells transduced with the gene for the B7.1 costimulatory molecule is potentially a good source of CTL for adoptive-transfer therapy of tumors.

**Adoptive -transfer therapy of tumors with the tumor -specific primary cytotoxic T cells induced in vitro with the B7.1-transduced MCA205 cell line.**

AUTHOR: Jung Kim Sun; Sadelain Michel; Lee Jeong-Soon; Hyun Seong Roh; Yun Yeon-Sook; Ju Jang Young; Yong Chung Hee(a)

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JOURNAL: Cancer Immunology Immunotherapy 47 (5):p257-264 Jan., 1999

ISSN: 0340-7004

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

**ABSTRACT:** We show that the tumor-specific primary cytotoxic T lymphocytes (CTL) induced in vitro with the MCA205 fibrosarcoma cells transduced with the B7.1 (CD80) gene are highly effective in adoptive-transfer therapy of the parental tumors. The MCA205 fibrosarcoma cell line was transduced with the retroviral vectors encoding the B7.1 gene and tested for their efficiency as stimulators in short-term (5 days) mixed lymphocyte/tumor cell cultures with highly purified syngenic, unprimed T cells as responders. The induction of the CTL required the presence of a low dose of interleukin-2 (25 U/ml). The injection of the CTL prevented colony

formation by the intravenously injected tumor cells in a lung colonization assay in which the CTL were injected after inoculation of tumor cells. We also showed that the adoptive transfer of the same T cells was effective in delaying the growth of the subcutaneously injected tumor cells. These results imply that the short-term mixed lymphocyte/tumor cell culture with the tumor cells transduced with the gene for the B7.1 costimulatory molecule is potentially a good source of CTL for adoptive-transfer therapy of tumors.

**Activation of T lymphocytes for the adoptive immunotherapy of cancer.**

Sussman J J; Shu S; Sondak V K; Chang A E

Division of Surgical Oncology, University of Michigan, Ann Arbor.

Annals of surgical oncology: the official journal of the Society of  
Surgical Oncology (UNITED STATES) Jul 1994, 1 (4) p296-306, ISSN  
1068-9265 Journal Code: 9420840

Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

BACKGROUND: Adoptive immunotherapy of malignancy involves the passive transfer of antitumor-reactive cells into a host in order to mediate tumor regression. Based on animal models, the transfer of immune lymphoid cells can eradicate widely disseminated tumors and establish long-term systemic immunity. Critical for successful adoptive immunotherapy is the ability to isolate large numbers of immune cells. For clinical therapy, it will require the development on **in vitro** methods to promote the sensitization and propagation of tumor-reactive cells. However, this is a formidable task since human cancers are postulated to be poorly immunogenic because of their spontaneous origins. RESULTS: Human lymphoid cells for **ex vivo** activation and subsequent **adoptive** transfer have been derived from different sources, including peripheral blood, tumor, and lymph nodes. Peripheral blood lymphocytes c **Lymphokine-activated killer (LAK) cells**. Analysis of fa  
**the immunotherapy of human cancer.**

Rayner A A; Grimm E A; Lotze M T; Chu E W; Rosenberg S A

Cancer (UNITED STATES) Mar 15 1985, 55 (6) p1327-33, ISSN 0008-543X  
Journal Code: 0374236

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Lymphokine-activated killer (LAK) cells can be generated by incubating fresh peripheral blood lymphocytes (PBL) in Interleukin-2 (IL-2). LAK cells kill fresh autologous and allogeneic human tumor cells **in vitro**. This study analyzes aspects of LAK cells that make them a promising candidate for the **adoptive** immunotherapy of human cancer. LAK cells can be generated from PBL of normal individuals and tumor-bearing patients. Pure, recombinant IL-2 generates LAK cells capable of killing a wide variety of tumors including sarcomas and cancers of the colon, pancreas, adrenal gland, and esophagus. Thirty-six of 41 (88%) fresh, noncultured, human tumor cell suspensions prepared from surgical specimens were lysed by LAK cells in a standard 4-hour chromium-release assay. Normal PBL were not killed. LAK cells can be expanded **in vitro** for periods longer than 2 months, potentially more than 10(20)-fold, while maintaining lytic ability. These results and the demonstrated efficacy of **LAK** cells in the **therapy** of murine **tumors** make **LAK** cells a candidate for clinical use in the **adoptive** immunotherapy of human cancer.

10/3,AB/19 (Item 19 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

Set Items Description

S1	3399	(LYMPHOCYTE OR (T (W) CELL?)) (2N) (THERAP?) (5N) (TUMOR? - OR CANCER?)
S2	320	S1 (S) (ADOPTIVE OR (EX (W) VIVO))
S3	216	S2 NOT PY>1999
S4	88	RD (unique items)
S5	36	S4 (S) (CULTUR? OR (IN(W)VITRO))
S6	528	(LAK OR NK) (2N) (THERAP?) (5N) (TUMOR? OR CANCER)
S7	159	S6 (S) (ADOPTIVE OR (EX (W) VIVO))
S8	81	S7 (S) (CULTUR? OR (IN (W) VITRO))
S9	24	RD (unique items)
S10	24	S9 NOT PY>1999

Adoptive -transfer therapy of tumors with the tumor -specific primary cytotoxic T cells induced in vitro with the B7.1-transduced MCA205 cell line.

Kim S J; Sadelain M; Lee J S; Seong R H; Yun Y S; Jang Y J; Chung H Y  
Laboratory of Tumor Immunology, Korea Cancer Center Hospital, Seoul.  
Cancer immunology, immunotherapy : CII (GERMANY) Jan 1999, 47 (5)

p257-64, ISSN 0340-7004 Journal Code: 8605732

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

We show that the tumor-specific primary cytotoxic T lymphocytes (CTL) induced in vitro with the MCA205 fibrosarcoma cells transduced with the B7.1 (CD80) gene are highly effective in adoptive-transfer therapy of the parental tumors. The MCA205 fibrosarcoma cell line was transduced with the retroviral vectors encoding the B7.1 gene and tested for their efficiency as stimulators in short-term (5 days) mixed lymphocyte/tumor cell cultures with highly purified syngenic, unprimed T cells as responders. The induction of the CTL required the presence of a low dose of interleukin-2 (25 U/ml). The injection of the CTL prevented colony formation by the intravenously injected tumor cells in a lung colonization assay in which the CTL were injected after inoculation of tumor cells. We also showed that the adoptive transfer of the same T cells was effective in delaying the growth of the subcutaneously injected tumor cells. These results imply that the short-term mixed lymphocyte/tumor cell culture with the tumor cells transduced with the gene for the B7.1 costimulatory molecule is potentially a good source of CTL for adoptive-transfer therapy of tumors.

#### Tumor reactivity of immune T cells in short-term culture.

Krauss J C; Stein J M; Shu S

Center for Surgery Research/FF-50, Cleveland Clinic Foundation, OH 44195, USA. kraussj@cesmtp.ccl.org

Cancer immunology, immunotherapy : CII (GERMANY) Dec 1996, 43 (4)

p231-9, ISSN 0340-7004 Journal Code: 8605732

Contract/Grant No.: CA 58927; CA; NCI; CA 67324; CA; NCI; HL-027640; HL; NHLBI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The adoptive transfer of immune T cells is capable of mediating the regression of established neoplasms in a variety of animal tumor models. The antitumor

Current status of adoptive immunotherapy of cancer.

Chang A E; Shu S

Department of Surgery, University of Michigan, Ann Arbor 48109, USA.

Critical reviews in oncology/hematology (IRELAND) Apr 1996, 22 (3)

p213-28, ISSN 1040-8428 Journal Code: 8916049

Document type: Journal Article; Review; Review, Academic

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The sentinel observations made by William B. Coley, M.D. in the 1890s that patients with malignancies can respond to the intratumoral inoculation of live bacterial organisms or bacterial toxins became the cornerstone for the development of immunotherapy for cancers. It has been repeatedly demonstrated that tumors express unique proteins which can trigger an immune response. The adoptive transfer of immune cells to the host with established malignancy can mediate complete eradication of local or disseminated tumors and result in systemic immunity. This review summarizes the current experimental as well as clinical status of adoptive immunotherapy of cancer. There are a number of different methods to isolate tumor-reactive T cells from the tumor-bearing host and allow for their *ex vivo* expansion. A new direction in this field includes attempts to up-regulate the immunogenicity of tumors by genetically modifying tumor cells to express immunoregulatory peptides (i.e. cytokines, co-stimulatory molecules, etc.) in order to exploit endogenously weak immune responses to autochthonous tumors. Other new directions involve developing methods to generate or isolate tumor-reactive T cells subsets by selective *in vitro* stimulation (i.e. bacterial superantigens) or genetic engineering of

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## ARTICLES

### Activation of T lymphocytes for the adoptive immunotherapy of cancer

**J. J. Sussman, S. Shu, V. K. Sondak and A. E. Chang**

Division of Surgical Oncology, University of Michigan, Ann Arbor.

**BACKGROUND:** Adoptive immunotherapy of malignancy involves the passive transfer of antitumor-reactive cells into a host in order to mediate tumor regression. Based on animal models, the transfer of immune lymphoid cells can eradicate widely disseminated tumors and establish long-term systemic immunity. Critical for successful adoptive immunotherapy is the ability to isolate large numbers of immune cells. For clinical therapy, it will require the development on in vitro methods to promote the sensitization and propagation of tumor-reactive cells. However, this is a formidable task since human cancers are postulated to be poorly immunogenic because of their spontaneous origins. **RESULTS:** Human lymphoid cells for ex vivo activation and subsequent adoptive transfer have been derived from different sources, including peripheral blood, tumor, and lymph nodes. Peripheral blood lymphocytes can be incubated with interleukin 2 to generate lymphokine-activated killer (LAK) cells, which nonspecifically lyse autologous and allogeneic tumor cells in vitro. LAK cell therapy represented the earliest attempt to treat advanced human cancers, with encouraging results documented in patients with renal cell cancer and melanoma. From that experience, the use of more immunologically specific cellular agents with potentially greater therapeutic efficacy has been investigated. One approach uses tumor-infiltrating lymphocytes, which have been characterized experimentally to be more specific in tumor reactivity compared with LAK cells. Other techniques have involved the use of lymphoid cells derived from lymph nodes draining tumors or primed by tumor vaccines. In vitro activation of these cells with tumor antigen or anti-CD3 monoclonal antibody results in the generation of T cells that mediate the rejection of poorly immunogenic tumors in animal studies. These alternate methods are currently being evaluated in clinical studies. **CONCLUSIONS:** Experimentally, cellular therapy is a potent method to eradicate progressive tumors. Initial clinical studies have demonstrated that this form of therapy is technically feasible and can result in meaningful antitumor responses. Advances in this area will require improved methods to sensitize, isolate, and expand tumor-reactive T cells for adoptive transfer.

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